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ABSTRACT

No systematic study of circadian cycles of lung functions has been reported in the literature in which environmental influences were rigidly controlled. Vital capacity inspiratory capacity, expiratory reserve volume, maximum expiratory flow rate and maximum inspiratory flow rate were measured four times daily at four-hour intervals in two subjects during a control period, during nine days of isolation in a constant environment, and during a three-day recovery period. Temperature was kept at 27°C ± 0.1°, barometric pressure 30.560 ± .004 inches. All the lung functions measured showed circadian cycles which shifted during the isolation period in the same direction as sleep-wakefulness cycles, but at a somewhat different rate. Periodicities were determined with a computer analysis, using a cross-correlation technique with a synthesized 24-hour sinusoid. Average daily variability of lung functions based on circadian cycles ranged from 5.6 ± 1.7% for vital capacity, to 20.3 ± 10.4% for maximum inspiratory flow rate.

Key words: variability of respiratory functions, circadian cycles; isolation in constant environment

VARIABILITY OF RESPIRATORY FUNCTIONS
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A knowledge of the variability of lung functions is essential for an accurate evaluation of respiratory abnormalities. Day-to-day changes in lung functions have been reported in normal subjects and in patients with cardiorespiratory diseases by Shepard et al (10) and Spicer et al (11, 12).

The observed daily changes in respiratory functions could be related either to environmental changes or to cyclic changes of an endogenous nature (circadian cycles). A significant correlation was established between changes of respiratory functions and alterations in atmospheric conditions (10) and more specifically with the temperature of the environment outside on the day of measurement (12). However, no systematic study of diurnal cycles of lung functions has been reported in which the environmental influences were rigidly controlled. This report presents results of such an investigation, carried out as part of a larger study on effects of isolation in a constant environment on circadian cycles of physiological functions. (9).

METHODS

Two medical students, ages 23 and 24, served as subjects. They were both highly motivated and well acquainted with the equipment. Following a control period of four days, the two subjects were exposed to a constant environment in a pressure-altitude chamber in which the following conditions were maintained; Temperature, 27°C $\pm$ 0.1°; humidity, 30% $\pm$ 5%; barometric pressure, 30.560 $\pm$ .004 inches. More details about the chamber operations are given elsewhere (3).

The subjects gave information about getting up, meals, bed time, lung function tests and phychomotor tests, as well as collection of saliva and urine samples, through a microphone to the control room, and recorded these items in their log books. During the isolation period, messages from the control room were relayed to the subjects in code signals. The subjects were unable to hear any noise from the outside when the chamber was closed. They prepared their own meals from Army C rations, which were found highly acceptable.

Lung volumes, vital capacity (VC), inspiratory capacity (IC), expiratory reserve volume (ERV), maximal inspiratory flow rate (MIFR), and maximal expiratory flow rate (MEFR) were determined by the velocity-volume technique developed by Bartlett (2). A Wedge spirometer (Model 370 by Med-Science Electronics), a Tektronic Type 520 A Dual-beam Oscilloscope and a Polaroid camera with a special lens were utilized. The bellows component of the spirometer was placed inside the environmental chamber. The six-wire shielded cable, connecting the bellows to the power supply-amplifier unit, was cut and modified to allow the electrical signal to pass through the chamber wall. The power supply-amplifier unit, the oscilloscope, and the camera were outside the chamber. Instructions were given to the subjects, during the control period, by the use of an intercom and, during isolation, through a previously tested audio code.

The subject, while wearing a noseclip, was instructed to commence breathing, normally, into the spirometer. After the small tidal volume loops began to retrace themselves, one was photographed. Instructions to expire completely were given, the camera shutter was opened at the end of expiration, then the subject was told to inspire as rapidly and completely as possible. Following this a rapid, complete expiration was performed, with the shutter still open. The result is a photograph showing a tidal loop and a maximal inspiratory-expiratory loop. Vital capacity, inspiratory capacity, expiratory reserve volume, maximal expiratory flow rate, and maximal inspiratory flow rate were determined from the photograph. The flow rates utilized represent an instantaneous peak flow rate.

To avoid influence of meals, measurements were made four times daily, prior to breakfast, lunch, supper, and before going to bed. On the second day of isolation, no determinations were made for external reasons. The two subjects were trained, prior to the experiment, in this technique until reproducible results were obtained. As a standard procedure, duplicate tests were carried out by each subject during each sampling period The greater of the two values was utilized, since the method involved the measurement of a maximum effort. The measured data were corrected to B.T.P.S., using the body temperature data (rectal temperature) which were telemetered during the experiment simultaneously with the lung function tests. The average daily variations from the mean values measured during isolation were expressed in per cent of the mean values.

The periodicities of lung functions, in the range of 24 hours, were determined with a computer analysis involving cross-correlation of data with a synthesized 24-hour sinusoid of known amplitude and phase (4). Vital statistics of the two subjects are presented in Table 1. Measured data on lung volumes and flow rates, obtained during the control period, were averaged and compared with predicted data for the two subjects, based on sex, age, height, and weight, Table 2. Vital capacity, expiratory reserve volume and maximum expiratory flow rates of the tall subject (DA) were so large as to be outside the normal range while those of the smaller subject (GR) were slightly above the predicted average, but within normal range with the exception of the maximal expiratory flow rates.

RESULTS

During the period of isolation, average daily values of lung volumes and flow rates did not change significantly compared with data obtained during control and recovery periods. Figure 1 shows the daily changes of vital capacity, inspiratory capacity and expiratory reserve volume. To evaluate these data, it is important to note that the subjects shifted, on the average, 1.6 hours per day during the isolation period, getting up later and going to bed later, which is indicated in Figure 1 in the shift of the sleeping period (black bars). All three functions (VC, IC, ERV) exhibit clearly cyclic changes with a minimum appearing more frequently shortly after awakening and a maximum later in the day. This cyclic pattern is generally maintained throughout the isolation period. That means the cycles of lung functions shift with the sleep-wakefulness cycles. At the eighth day of isolation, the morning values of the expiratory reserve volume are maximal or near maximal in the two subjects. Following the isolation period, the subjects returned within a day, to their normal time schedule by increasing their activity period to over 30 hours. On the first morning of the recovery period, most of the data of the

Three lung volumes are in the range of maximal daily values (measured during isolation). but during the subsequent two days data indicated a trend towards re-establishing the cyclic pattern with a minimum after awakening.

Figure 2 exhibits the daily changes of maximum inspiratory and expiratory flow rates. Both of these functions show similar cyclic changes as VC, IC, and ERV, and the cycles also shift during isolation with the sleep-wakefulness cycle.

In Figure 3, the shift in sleep-wakefulness cycle during the isolation period is plotted together with the daily shift of the maxima of vital capacity, maximal expiratory and inspiratory flow rates of the two subjets. The maxima of the depicted functions shift in general with the sleep-wakefulness cycle. However. at the sixth and seventh day of isolation the shift of vital capacity becomes less than that of the sleep-wakefulness cycle. The periodicities of lung functions (cyclic length) measured during the isolation period are shown in Table 3. They are mostly between 24 and 25 hours in both subjects.

Table 4 presents the average daily variation of lung functions and flow rates which correspond closely between the two subjects. Variability of VC is less than that of IC and ERV, the latter showing the largest changes (10-20%). Daily variations of the flow rates are even larger, reaching 18 to 20 % for MIFR. Under conditions of our experiment (isolation in a constant environment) the average daily variations, presented in Table 4, represent the average amplitudes of circadian cycles of lung function and flow rates. Subject GR, who exhibits the larger amplitudes in IC and flow rates, also showed larger amplitudes of cycles in body temperature, pulse rate, and respiratory rate (9).

DISCUSSION

Diurnal cycles of vital capacity, with a minimum after midnight, have been observed in healthy men by Kroetz (5) and Menzel (9). More recently, measurements of airway resistance four times a day during a two-day period also demonstrated the existence of circadian cycles (6). These observations were made under conditions in which the normal environmental influences were present. Our findings on regular daily variations of lung functions and flow rates in a constant environment clearly establish the persistence of spontaneous rhythms of these functions when the environmental influences are eliminated. The cycles of lung functions were shown to be "free running' rhythms, as indicated in the shift of the maxima across the local time scale. The calculated free running, or spontaneous, periodicities average between 24 and 25 hours, corresponding with free running (circadian) cycles reported in human subjects (1,7).

The evidence for regular spontaneous cyclic variations in respiratory functions has a bearing on the establishment of normal standards for the measurement of respiratory functions. To our knowledge, the literature does not contain any references to the variability of respiratory functions based on circadian cycles. This is the first report containing such information. Although it is limited to two subjects, it does provide some guide posts. Further investigations on a larger number of healthy subjects, and patients with respiratory diseases, should be made. To detect abnormalities in respiratory function of subjects and to measure the effects of drugs or various environmental agents (air pollution) with some degree of reliability, it is essential to take the inherent cyclic variability of respiratory functions into account. This aspect appears to be of particular significance for the evaluation of changes in lung functions of astronauts exposed for prolonged periods to pure oxygen at reduced barometric pressures or aquanauts exposed to high pressures in an artificial environment.

The diurnal changes of vital capacity in healthy subjects have been considered to be related to the changes in blood content of the pulmonary vessels, which increase during the night (8). It is not known to what extent the circadian circulatory alterations are also associated with the circadian cycles in maximal expiratory and inspiratory flow rates.

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TABLE 1

VITAL STATISTICS OF SUBJECTS

	Subject DA	Subject GR
Age (years)	23	24
Height (inches)	75	68
Weight (pounds)	200	160
Surface areas (M^2)	2.21	1.86

TABLE 2

MEASURED AND PREDICTED LUNG VOLUMES AND FLOW RATES

	Subject DA			Subject GP		
	Measured Values	Predicted Values (and ranges)	Measured Values in Per Cent of Predicted Values	Measured Values	Predicted Values (and ranges)	Measured Values in Per Cent of Predicted Values
Vital capacity (liters)	7.241*	5.890 (4.730-7.050)	123%*	5.373	4.920[1] (3.76-6.080)	109%
S.D.	.150			.128		
Inspiratory capacity (liters)	4.637	4.185	111%	3.474	3.386[1&2]	103%
S.D.	.369			.280		
Expiratory Reserve Volume	2.861	1.805 (1.125-2.485)	159%*	1.189	1.534[2]	123%
S.D.	.202			.230		
Maximum Expiratory Flow Rate (L/sec)	12.69	9.0 (7.0-11.0)	141%*	12.07*	9.0 (7.0-11.0)	134%
S.D.	.78					
Maximum Inspiratory Flow Rate (L/sec)	10.59	> 5.0		8.80	> 5.0	
S.D.	.83			.94		

* Outside normal range

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TABLE 3

MEAN LENGTH (HR) OF THE "PHYSIOLOGICAL DAY" AS INDICATED IN CYCLE LENGTH OF LUNG FUNCTIONS AND FLOW RATES DURING ISOLATION IN A CONSTANT ENVIRONMENT

	N	Subject GK	Subject DA
Vital Capacity	7	23.6 ± 1.2	25.2 ± 1.6
Inspiratory Capacity	7	25.5 ± 1.0	25.6 ± 2.6
Expiratory Reserve Volume	7	25.1 ± 1.4	24.0 ± 2.2
Maximum Expiratory Flow Rate	7	24.1 ± 1.3	23.8 ± 1.6
Maximum Inspiratory Flow Rate	7	24.7 ± 1.3	25.0 ± 2.0

TABLE 4

AVERAGE DAILY VARIABILITY OF LUNG VOLUMES
AND FLOW RATES BASED ON CIRCADIAN CYCLES

Average of daily variations in per cent of mean

	N	Subject DA	Subject GR
Vital Capacity	7	5.58% ± 1.66%	4.11% ± 1.49%
Inspiratory Capacity	7	7.67% ± 2.96%	8.64% ± 4.39%
Expiratory Reserve Volume	7	12.50% ± 4.08%	10.52% ± 8.42%
Maximum Expiratory Flow Rate	7	9.53% ± 4.14%	10.61% ± 3.98%
Maximum Inspiratory Flow Rate	7	18.58% ± 7.31%	20.28% ± 10.4%

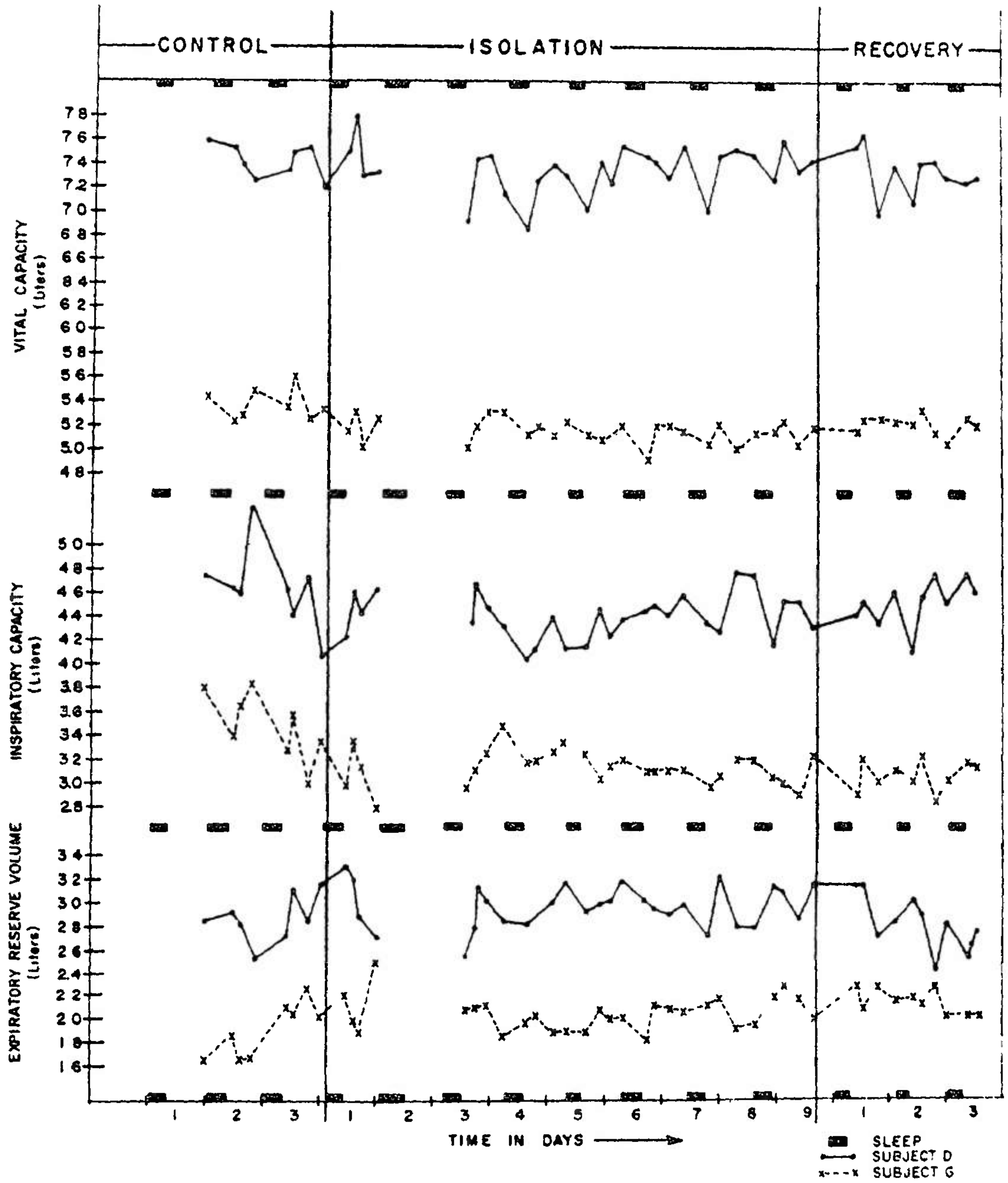

Figure 1. Daily changes of vital capacity, inspiratory capacity and expiratory reserve volume of two subjects during isolation in a constant environment.

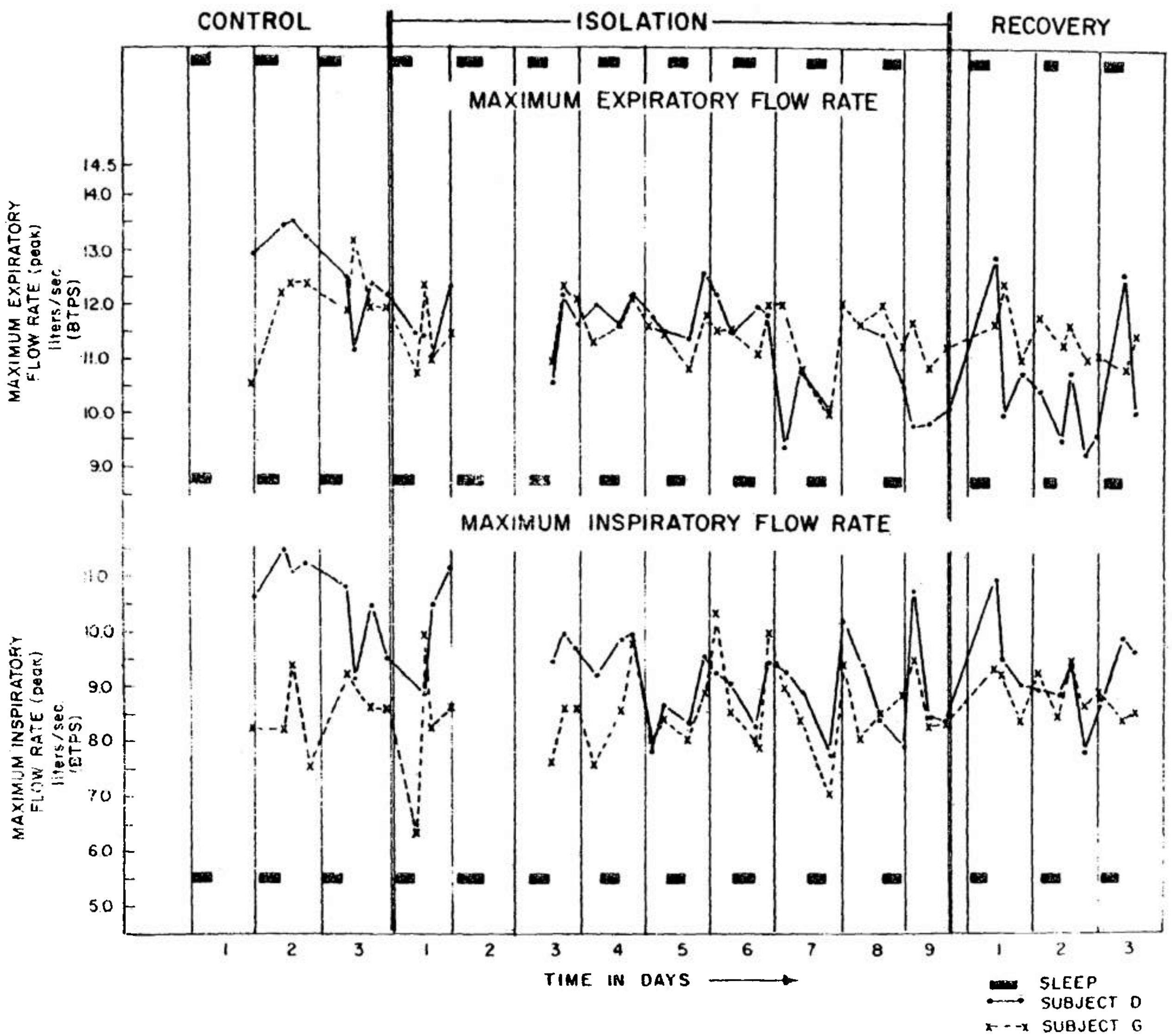

Figure 2. Daily changes of maximum inspiratory and expiratory flow rates of two subjects during isolation in a constant environment.

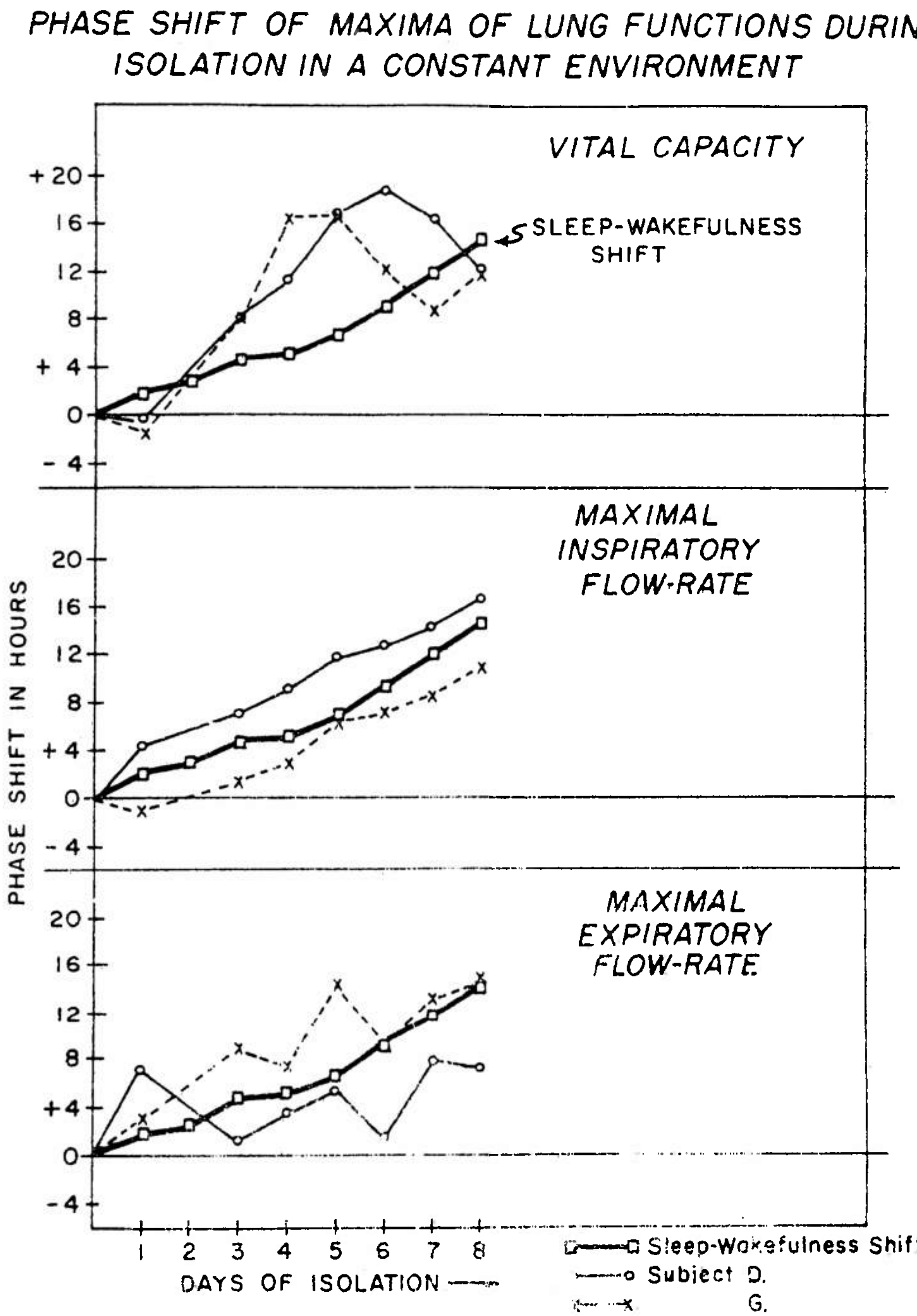

Figure 3. Daily shifts of the maxima of vital capacity, maximal inspiratory and expiratory flow rates during isolation in a constant environment and of the sleep-wakefulness cycle.